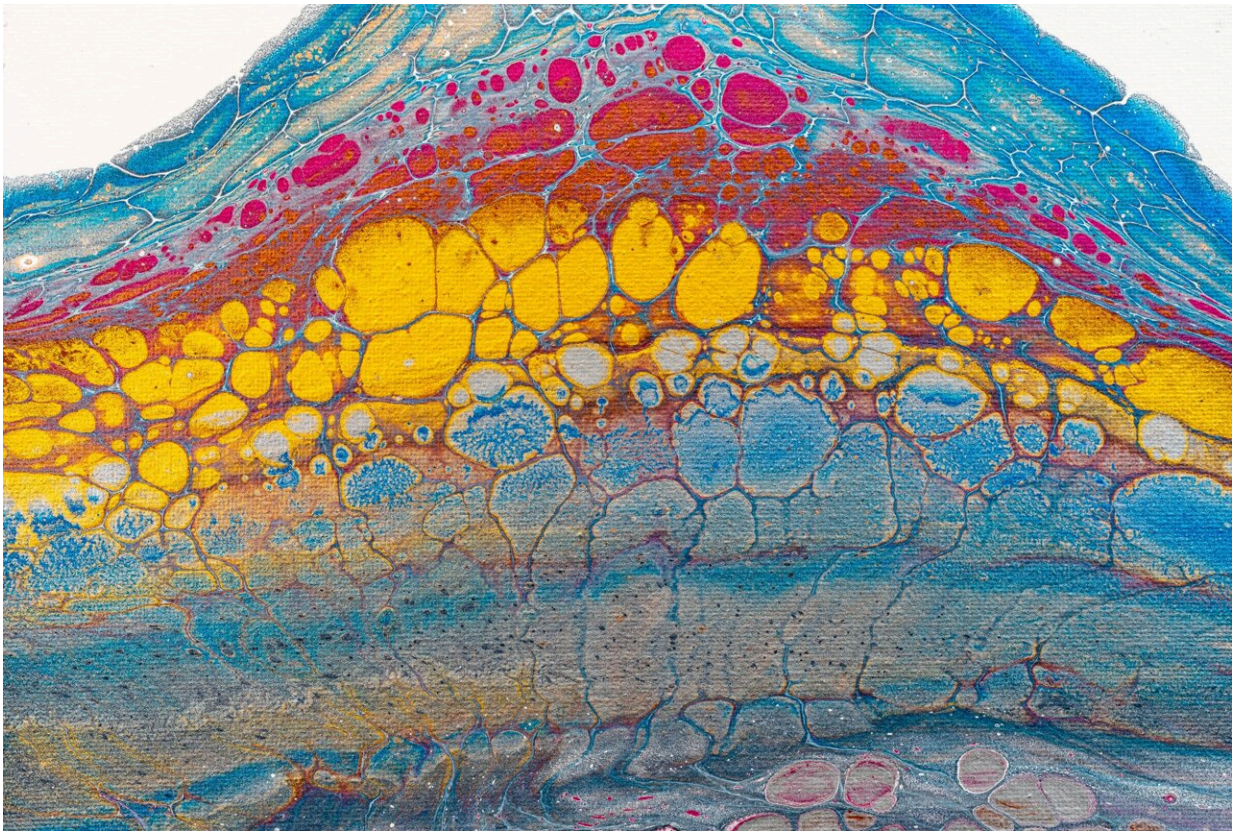
MedicalXpress

ASCO: Targeted therapy induces responses in HER2-amplified biliary tract cancer

June 3 2023



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HER2-targeted bispecific antibody zanidatamab demonstrated durable responses in patients with treatment-refractory HER2-positive biliary tract cancer (BTC), researchers from The University of Texas MD

Anderson Cancer Center reported at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting. The study results also were published today in *The Lancet Oncology*.

In the first cohort of the global Phase II HERIZON-BTC-01 trial, which included 80 patients with HER2-positive tumors, the confirmed objective response rate (cORR) was 41% with a median duration of response (DOR) of 12.9 months at a median follow-up of 12.4 months. Among the 33 responders, 49% had ongoing responses and 82% had a response lasting more than 16 weeks. This is the largest study of a HER2-targeted drug in BTC.

"Chemotherapy for patients with biliary tract cancers who have progressed on first-line therapy is usually associated with a 5% response rate," said global trial lead Shubham Pant, M.D., professor of Gastrointestinal Medical Oncology and Investigational Cancer Therapeutics. "These results provide evidence that zanidatamab can achieve durable responses and may offer a new treatment opportunity for patients who previously had limited options."

Patients with advanced BTC who progress after first-line treatment are offered standard-of-care therapies with limited clinical benefit and only modest improvement in survival. HER2-targeted therapies have improved survival in HER2-positive breast and gastric cancers, but there currently is no approved HER2-targeted therapy for BTC.

Zanidatamab was first evaluated in a Phase I trial led by Funda Meric-Bernstam, M.D., chair of Investigational Cancer Therapeutics. The trial results supported HER2 as an actionable target in various cancer types, including biliary tract cancer. Based on those results, MD Anderson researchers advanced zanidatamab into this Phase II trial for patients with BTC.

Biliary tract cancer, also known as cholangiocarcinoma, develops in the bile ducts, a series of thin tubes that run from the liver to the small intestine. There are three different types of BTC, whose names are based on the location where the cancer forms. According to the American Cancer Society, around 8,000 people in the U.S. are diagnosed each year with BTC. However, the true count likely is higher because these cancers can be hard to diagnose and are often misclassified, Pant explained. The five-year survival rate for metastatic BTC is less than 5%, highlighting an urgent need for new treatments.

This open-label, single-arm trial evaluated the anti-tumor activity of zanidatamab in patients with HER2-amplified advanced BTC, including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder cancer. The trial was conducted at 67 sites; patients were divided into two cohorts based on HER2 expression (positive or low/negative) by tumor immunohistochemistry. The primary endpoint was cORR in the HER2-positive cohort.

The study enrolled 80 patients in the HER2-positive cohort and seven patients in the HER2-low/negative cohort. All patients had received one previous line of gemcitabine-containing therapy. The median age was 64 years and patients were 65.5% Asian, 28.7% white and 5.7% other. Of the trial participants, 52% had gallbladder cancer, 30% had intrahepatic cholangiocarcinoma, and 18% had extrahepatic cholangiocarcinoma.

There were no responses to zanidatamab observed in the HER2-low/negative cohort. Across both cohorts, grade 3 treatment-related adverse events occurred in 18% of patients. Two patients (2.3%) discontinued zanidatamab due to an adverse event. No grade 4 or 5 treatment-related adverse events were reported.

"Given this data, we believe strongly that there should be continued efforts to explore zanidatamab as a viable treatment option for

HER2-positive biliary tract cancer," Pant said. "We are encouraged by the potential impact of zanidatamab on improving patient outcomes."

Pant and his team still are evaluating progression-free survival and overall survival in these patients. Additionally, clinical trials are underway to further investigate the therapeutic potential of zanidatamab as a monotherapy and in combination with first-line chemotherapy for HER2-positive BTC.

More information: James J Harding et al, Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study, *The Lancet Oncology* (2023). DOI: 10.1016/S1470-2045(23)00242-5

Provided by University of Texas M. D. Anderson Cancer Center